ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 0.25 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 0.25 mg cetrorelix (as acetate).
After reconstitution with the solvent provided, each mL of the solution contains 0.25 mg cetrorelix.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Appearance of the powder: white lyophilisate
Appearance of the solvent: clear and colourless solution

The pH of the reconstituted solution is 4.0-6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation, followed by oocyte pick-up and assisted reproductive techniques.

In clinical trials Cetrotide was used with human menopausal gonadotropin (HMG), however, limited experience with recombinant follicule-stimulating hormone (FSH) suggested similar efficacy.

4.2 Posology and method of administration

Cetrotide should only be prescribed by a specialist experienced in this field.

Posology
The first administration of Cetrotide should be performed under the supervision of a physician and under conditions where treatment of possible allergic/pseudo-allergic reactions (including life-threatening anaphylaxis) is immediately available. The following injections may be self-administered as long as the patient is made aware of the signs and symptoms that may indicate hypersensitivity, the consequences of such a reaction and the need for immediate medical intervention.

The contents of 1 vial (0.25 mg cetrorelix) are to be administered once daily, at 24 h intervals, either in the morning or in the evening. Following the first administration, it is advised that the patient be kept under medical supervision for 30 minutes to ensure there is no allergic/pseudo-allergic reaction to the injection.

Elderly
There is no relevant use of Cetrotide in the geriatric population.

Paediatric population
There is no relevant use of Cetrotide in the paediatric population.

Method of administration
Cetrotide is for subcutaneous injection into the lower abdominal wall.

The injection site reactions may be minimised by rotating the injection sites, delaying injection at the same site and injecting the product in a slow rate to facilitate the progressive absorption of the product.

Administration in the morning: Treatment with Cetrotide should commence on day 5 or 6 of ovarian stimulation (approximately 96 to 120 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period including the day of ovulation induction.

Administration in the evening: Treatment with Cetrotide should commence on day 5 of ovarian stimulation (approximately 96 to 108 hours after start of ovarian stimulation) with urinary or recombinant gonadotropins and is to be continued throughout the gonadotropin treatment period until the evening prior to the day of ovulation induction.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Cetrorelix is not to be used in the presence of any of the conditions listed below:

- Hypersensitivity to the active substance or any structural analogues of gonadotropin-releasing hormone (GnRH), extrinsic peptide hormones or to any of the excipients listed in section 6.1.
- During pregnancy and lactation.
- Patients with severe renal impairment.

4.4 Special warnings and precautions for use

Allergic conditions
Cases of allergic/pseudoallergic reactions, including life-threatening anaphylaxis with the first dose have been reported (see section 4.8).

Special care should be taken in women with signs and symptoms of active allergic conditions or known history of allergic predisposition. Treatment with Cetrotide is not advised in women with severe allergic conditions.

Ovarian Hyperstimulation Syndrome (OHSS)
During or following ovarian stimulation an ovarian hyperstimulation syndrome can occur. This event must be considered as an intrinsic risk of the stimulation procedure with gonadotropins

An OHSS should be treated symptomatically, e.g. with rest, intravenous electrolytes/colloids and heparin therapy.

Luteal phase support should be given according to the reproductive medical centre´s practice.

Repeated ovarian stimulation procedure
There is limited experience up to now with the administration of cetrorelix during a repeated ovarian stimulation procedure. Therefore cetrorelix should be used in repeated cycles only after a careful benefit/risk evaluation.

Congenital anomalies
The prevalence of congenital anomalies after the use of assisted reproductive technologies (ART) with or without GnRH antagonists may be slightly higher than after spontaneous conceptions although it is unclear whether this is related to factors inherent to the couple's infertility or the ART procedures. Limited data from clinical follow-up studies in 316 newborns of women administered cetrorelix for infertility treatments suggest that cetrorelix does not increase the risk of congenital anomalies in the offsprings.

Hepatic impairment
Cetrorelix has not been studied in patients with hepatic impairment and caution is therefore warranted.

Renal impairment
Cetrorelix has not been studied in patients with renal impairment and caution is therefore warranted. Cetrorelix is contraindicated in patients with severe renal impairment (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug-drug interaction studies have been performed with cetrorelix. *In vitro* investigations have shown that interactions are unlikely with medicinal products that are metabolised by cytochrome P450 or glucuronised or conjugated in some other way. However, the possibility of interactions with gonadotropins or medicinal products that may induce histamine release in susceptible individuals, cannot be totally excluded.

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding
Cetrotide is not intended to be used during pregnancy and lactation (see section 4.3).

Fertility
Studies in animals have indicated that cetrorelix exerts a dose related influence on fertility, reproductive performance and pregnancy. No teratogenic effects occurred when the medicinal product was administered during the sensitive phase of gestation.

4.7 Effects on ability to drive and use machines

Cetrotide has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions are local injection site reactions such as erythema, swelling and pruritus that are usually transient in nature and mild in intensity. In clinical trials, these effects were observed with a frequency of 9.4% following multiple injections of Cetrotide 0.25 mg.

Mild to moderate OHSS (WHO grade I or II) have been commonly reported and should be considered as an intrinsic risk of the stimulation procedure. Inversely, severe OHSS remains uncommon.

Uncommonly, cases of hypersensitivity reactions including pseudo-allergic/anaphylactoid reactions have been reported.

List of adverse reactions
The adverse reactions reported below are classified according to frequency of occurrence as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000).

Immune system disorders
Uncommon: Systemic allergic/pseudo-allergic reactions including life-threatening anaphylaxis.

Nervous system disorders
Uncommon: Headache

Gastrointestinal disorders
Uncommon: Nausea

Reproductive system and breast disorders
Common: Mild to moderate OHSS (WHO grade I or II) can occur which is an intrinsic risk of the stimulation procedure (see section 4.4).
Uncommon: Severe OHSS (WHO grade III)

General disorders and administration site conditions
Common: Local reactions at the injection site (e.g. erythema, swelling and pruritus).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Overdosage in humans may result in a prolonged duration of action but is unlikely to be associated with acute toxic effects.

In acute toxicity studies in rodents non-specific toxic symptoms were observed after intraperitoneal administration of cetrorelix doses more than 200 times higher than the pharmacologically effective dose after subcutaneous administration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-gonadotropin-releasing hormones, ATC code: H01CC02.

Mechanism of action
Cetrorelix is a luteinising hormone releasing hormone (LHRH) antagonist. LHRH binds to membrane receptors on pituitary cells. Cetrorelix competes with the binding of endogenous LHRH to these receptors. Due to this mode of action, cetrorelix controls the secretion of gonadotropins (LH and FSH).

Cetrorelix dose-dependently inhibits the secretion of LH and FSH from the pituitary gland. The onset of suppression is virtually immediate and is maintained by continuous treatment, without initial stimulatory effect.

Clinical efficacy and safety
In females, cetrorelix delays the LH surge and consequently ovulation. In women undergoing ovarian stimulation the duration of action of cetrorelix is dose dependent. At a dose of 0.25 mg per injection repeated injections every 24 hours will maintain the effect of cetrorelix.

In animals as well as in humans, the antagonistic hormonal effects of cetrorelix were fully reversible after termination of treatment.

5.2 Pharmacokinetic properties

Absorption
The absolute bioavailability of cetrorelix after subcutaneous administration is about 85%.

Distribution
The volume of distribution (V_d) is 1.1 L x kg^{-1}.

Elimination
The total plasma clearance and the renal clearance are 1.2 mL x min^{-1} x kg^{-1} and 0.1 mL x min^{-1} x kg^{-1}, respectively.
The mean terminal half-lives following intravenous and subcutaneous administration are about 12 h and 30 h, respectively, demonstrating the effect of absorption processes at the injection site.

Linearity
The subcutaneous administration of single doses (0.25 mg to 3 mg cetrorelix) and also daily dosing over 14 days show linear kinetics.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

No target organ toxicity could be observed from acute, subacute and chronic toxicity studies in rats and dogs following subcutaneous administration of cetrorelix. No signs of medicinal product-related local irritation or incompatibility were noted in dogs after intravenous, intraarterial and paravenous injection when cetrorelix was administered in doses clearly above the intended clinical use in man.

Cetrorelix showed no mutagenic or clastogenic potential in gene and chromosome mutation assays.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Mannitol

Solvent:
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial: 2 years

Reconstituted product: use immediately

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C); in the original package in order to protect from light. The unopened product may be stored in the original package at room temperature (not above 30°C) for up to three months.

This product must be at room temperature prior to injection. Remove from the refrigerator approximately 30 minutes before use.

Do not freeze or place next to the freezer compartment or a freezer pack.

6.5 Nature and contents of container

Powder: 2 ml vials (Type I glass) with a stopper (bromobutyl rubber) and flip-off aluminium cap.

1 vial contains 0.25 mg cetrorelix.

Solvent: Pre-filled syringe (Type I glass) with plunger stopper (siliconised bromobutyl rubber) and tip cap (polypropylene and styrene butadiene rubber).

1 pre-filled syringe contains 1 ml of water for injections.

Additionally for each vial the pack contains:

1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs

Pack sizes of 1 vial and 1 pre-filled syringe or 7 vials and 7 pre-filled syringes.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This product must be at room temperature prior to injection. Remove from the refrigerator approximately 30 minutes before use.

Cetrotide should only be reconstituted with the solvent provided, using a gentle, swirling motion. Vigorous shaking with bubble formation should be avoided.

The reconstituted solution is without particles and clear. Do not use if the solution contains particles or if the solution is not clear.

Withdraw the entire contents of the vial. This ensures a delivery to the patient of a dose of at least 0.23 mg cetrorelix.

The solution should be used immediately after reconstitution.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/001
EU/1/99/100/002

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 April 1999
Date of latest renewal: 13 April 2009

10. DATE OF REVISION OF THE TEXT

{DD/MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Merck KGaA,
Frankfurter Straße 250
D-64293 Darmstadt
Germany

B CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOX OF 1 VIAL AND 1 PRE-FILLED SYRINGE
BOX OF 7 VIALS AND 7 PRE-FILLED SYRINGES

1. NAME OF THE MEDICINAL PRODUCT

Cetrotide 0.25 mg powder and solvent for solution for injection
cetrorelix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial with powder contains:
0.25 mg cetrorelix (as acetate).

3. LIST OF EXCIPIENTS

Excipient: Mannitol.
Each pre-filled syringe with solvent contains: 1 mL water for injection.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for injection.
1 pre-filled syringe with solvent for parenteral use.
Additionally, the pack contains:
1 injection needle (20 gauge)
1 hypodermic injection needle (27 gauge)
2 alcohol swabs.

7 vials with powder for solution for injection.
7 pre-filled syringes with solvent for parenteral use.
Additionally, the pack contains:
7 injection needle (20 gauge)
7 hypodermic injection needle (27 gauge)
14 alcohol swabs.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C). Keep the vial in the original package in order to protect from light. The unopened product may be stored in the original package at room temperature (not above 30°C) for up to three months. Do not freeze or place next to the freezer compartment or a freezer pack.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Europe B.V.
Gustav Mahlerplein 102
1082 MA Amsterdam
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/99/100/001
EU/1/99/100/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

cetrotide 0.25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier code

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CETROTIDE 0.25 MG VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Cetrotide 0.25 mg powder for solution for injection
cetrorelix
Subcutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.25 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for Cetrotide 0.25 mg
Water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Cetrotide 0.25 mg powder and solvent for solution for injection
Cetrorelix acetate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Cetrotide is and what it is used for

What Cetrotide is
Cetrotide contains a medicine called ‘cetrorelix acetate’. This medicine stops your body from releasing an egg from your ovary (ovulation) during your menstrual cycle. Cetrotide belongs to a group of medicines called ‘anti-gonadotropin-releasing hormones’.

What Cetrotide is used for
Cetrotide is one of the medicines used during ‘assisted reproductive techniques’ to help you get pregnant. It stops eggs being released straight away. This is because if the eggs are released too early (premature ovulation) it may not be possible for your doctor to collect them.

How Cetrotide works
Cetrotide blocks a natural hormone in your body called LHRH (‘luteinising hormone releasing hormone’).
- LHRH controls another hormone, called LH (‘luteinising hormone’).
- LH stimulates ovulation during your menstrual cycle.

This means that Cetrotide stops the chain of events that leads to an egg being released from your ovary. When your eggs are ready to be collected, another medicine will be given to you that will release them (ovulation induction).

2. What you need to know before you use Cetrotide

Do not use Cetrotide

- if you are allergic to cetrorelix acetate or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to medicines similar to Cetrotide (any other peptide hormones).
- if you are pregnant or breast-feeding.
- if you have severe kidney disease.

Do not use Cetrotide if any of the above applies to you. If you are not sure, talk to your doctor before using this medicine.

Warnings and precautions

Allergies
Tell your doctor before using Cetrotide if you have an active allergy or have had allergies in the past.

Ovarian Hyperstimulation Syndrome (OHSS)
Cetrotide is used together with other medicines that stimulate your ovaries to develop more eggs ready to be released. During or after you receive these medicines, you may develop Ovarian Hyperstimulation Syndrome (OHSS). This is when your follicles develop too much and become large cysts.
For possible signs to look out for and what to do if this happens see section 4 '*Possible side effects*'.

Using Cetrotide during more than one cycle
Experience of using Cetrotide during more than one cycle is small. Your doctor will carefully look at the benefits and risks for you, if you need to have Cetrotide during more than one cycle.

Liver disease
Tell your doctor before using Cetrotide if you have a liver disease. Cetrotide has not been investigated in patients with hepatic disease.

Kidney disease
Tell your doctor before using Cetrotide if you have a kidney disease. Cetrotide has not been investigated in patients with kidney disease.

Children and adolescents
Cetrotide is not indicated for the use in children and adolescents.

Other medicines and Cetrotide
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
Do not use Cetrotide if you are pregnant, think you may be pregnant, or if you are breast-feeding.

Driving and using machines
Cetrotide is not expected to affect your ability to drive and use machines.

3. How to use Cetrotide

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Using this medicine
This medicine is only for injection just under the skin of your belly (subcutaneous). To reduce skin irritation, select a different part of your belly each day.

- Your doctor must supervise your first injection. Your doctor or nurse will show you how to prepare and inject the medicine.
- You can carry out the following injections yourself as long as your doctor has made you aware of the symptoms that may indicate allergy and of the possibly serious or life threatening consequences that would need immediate treatment (see section 4 '*Possible side effects'*).
- Please carefully read and follow the instructions at the end of this leaflet called *'How to mix and inject Cetrotide'*.

- You start by using another medicine on day 1 of your treatment cycle. You then start using Cetrotide a few days later. (See next section *'How much to use'*).

How much to use
Inject the contents of one vial (0.25 mg Cetrotide) once each day. It is best to use the medicine at the same time each day, leaving 24 hours between each dose.

You can choose to inject every morning **or** every evening.
- If you are injecting every morning: Start your injections on day 5 or 6 of the treatment cycle. Your doctor will tell you the exact date and time. You will keep using this medicine up until and including the morning that your eggs are collected (ovulation induction).

OR
- If you are injecting every evening: Start your injections on day 5 of the treatment cycle. Your doctor will tell you the exact date and time. You will keep using this medicine up until and including the evening before your eggs are collected (ovulation induction).

If you use more Cetrotide than you should
Bad effects are not expected if you accidentally inject more of this medicine than you should. The effect of the medicine will last for longer. No specific measures are usually required.

If you forget to use Cetrotide
- If you forget a dose, inject it as soon as you remember and talk to your doctor.
- Do not inject a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions
- Warm, red skin, itching (often in your groin or armpits), red, itchy, raised areas (hives), runny nose, fast or uneven pulse, swelling of your tongue and throat, sneezing, wheezing or serious difficulty breathing, or dizziness. You may be having a possible serious, life-threatening allergic reaction to the medicine. This is uncommon (may affect up to 1 in 100 women).

If you notice any of the side effects above, stop using Cetrotide and contact your doctor immediately.

Ovarian Hyperstimulation Syndrome (OHSS)
This may occur due to the other medicines that you are using to stimulate your ovaries.
- Lower abdominal pain together with feeling sick (nausea) or being sick (vomiting) may be the symptoms of Ovarian Hyperstimulation Syndrome (OHSS). This may indicate that the ovaries over-reacted to the treatment and that large ovarian cysts developed. This event is common (may affect up to 1 in 10 women).
- The OHSS may become severe with clearly enlarged ovaries, decreased urine production, weight gain, difficulty breathing or fluid in your stomach or chest. This event is uncommon (may affect up to 1 in 100 women).

If you notice any of the side effects above, contact your doctor immediately.

Other side effects
<u>Common (may affect up to 1 in 10 women):</u>
- Mild and short lasting skin irritation may occur at the injection site like redness, itching or swelling.

Uncommon (may affect up to 1 in 100 women):
- Feeling sick (nausea)
- Headache.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Cetrotide

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial after EXP. The expiry date refers to the last day of that month.
The Cetrotide powder in the vial and the sterile water (solvent) in the pre-filled syringe have the same expiry date. It is printed on the labels and on the packaging.

Store in a refrigerator (2°C – 8°C).
The unopened product may be stored in the original package at room temperature (not above 30°C) for up to three months.

Do not freeze or place next to the freezer compartment or a freezer pack.

Keep the vial in the original package in order to protect from light.

The solution should be used immediately after preparation.

Do not use this medicine if you notice that the white pellet in the vial has changed in appearance. Do not use it if the prepared solution in the vial is not clear and colourless or if it has particles in it.

Do not throw any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Cetrotide contains
- The active substance is cetrorelix acetate. Each vial contains 0.25 mg cetrorelix acetate.
- The other ingredient is mannitol.
- The solvent is water for injection.

What Cetrotide looks like and contents of the pack
Cetrotide is a white powder for solution for injection in a glass vial with a rubber stopper. It is available in packs of one or seven vials (not all pack sizes may be marketed).

For each vial, the packs contain:
- one syringe pre-filled with sterile water for injection (solvent). This water is for mixing the powder in the vial
- one needle with a **yellow** mark - for injecting the sterile water into the vial and drawing the made up medicine out from the vial
- one needle with a **grey** mark - for injecting the medicine into your belly
- two alcohol swabs for cleaning

Marketing Authorisation Holder
Merck Europe B.V., Gustav Mahlerplein 102, 1082 MA Amsterdam, The Netherlands

Manufacturer
Merck KGaA, Frankfurter Straße 250, D-64293 Darmstadt, Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu.

HOW TO MIX AND INJECT CETROTIDE

- This section tells you how to mix the powder and the sterile water (solvent) together and then how to inject your medicine.
- Before starting to use this medicine, please read these instructions the whole way through first.
- This medicine is only for you – do not let anyone else use it.
- Use each needle, vial and syringe only once.

Before you start

1. **This product must be at room temperature prior to injection. Remove from the refrigerator approximately 30 minutes before use.**

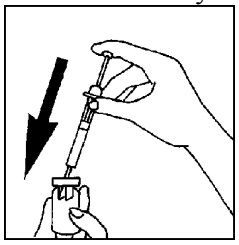
2. **Wash your hands**
   - It is important that your hands and the things you use are as clean as possible.

3. **Lay out everything you need on a clean surface:**
   - one vial of powder
   - one syringe pre-filled with sterile water (solvent)
   - one needle with a **yellow** mark – for injecting the sterile water into the vial and drawing the made-up medicine out from the vial
   - one needle with a **grey** mark – for injecting the medicine into your belly
   - two alcohol swabs.

Mixing the powder and water to make up your medicine

1. **Remove the cap from the vial**
   - There will be a rubber stopper underneath – keep this in the vial.
   - Wipe the rubber stopper and metal ring with your first alcohol swab.

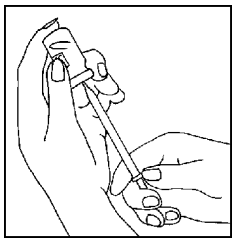
2. **Adding the water from the pre-filled syringe to the powder in the vial**
   - Unwrap the needle with the **yellow** mark on it.
   - Remove the cap from the pre-filled syringe and screw the yellow needle onto it. Remove the cap from the needle.
   - Push the yellow needle through the centre of the rubber stopper of the vial.
   - Slowly push in the plunger of the syringe to inject the water into the vial. Do not use any other sort of water.
   - Leave the syringe in the rubber stopper.



3. **Mixing the powder and water in the vial**
   - While carefully holding the syringe and vial, swirl gently to mix the powder and water together. When it is mixed, it will look clear and have no particles in it.
   - Do not shake or you will create bubbles in your medicine.

4. **Re-filling the syringe with the medicine from the vial**
   - Turn the vial upside down.
   - Pull the plunger out to draw the medicine from the vial back into the syringe.

- If any medicine is left in the vial, pull out the yellow needle until the end of the needle is just inside the rubber stopper. If you look from the side through the gap in the rubber stopper, you can control the movement of the needle and the liquid.
- Make sure that you collect all of your medicine from the vial.

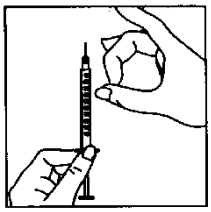


- Put the cap back on the yellow needle. Unscrew the yellow needle from the syringe and lay down the syringe.

Preparing the injection site and injecting your medicine

1. Removing air bubbles

- Unwrap the needle with the **grey** mark on it. Screw the grey needle onto the syringe and remove the cap from the grey needle.
- Hold the syringe with the grey needle pointing upwards and check for any air bubbles.
- To remove air bubbles, gently flick the syringe until all the air collects at the top - then slowly push the plunger in until the air bubbles are gone.
- Do not touch the grey needle and do not let the needle touch any surface.

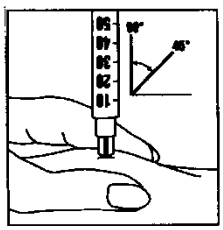


2. Clean the injection site

- Choose an injection site on your belly. It is best around the belly button (navel). To reduce skin irritation, select a different part of your belly each day.
- Clean the skin at your chosen injection site with your second alcohol swab - use a circular motion.

3. Piercing your skin

- Hold the syringe in one hand – like you would hold a pencil.
- Gently pinch up the skin around where you are going to inject and hold this firmly with your other hand.
- Slowly push the grey needle completely into your skin at an angle of about 45 to 90 degrees – then let go of your skin.



4. Injecting your medicine

- Gently pull back the plunger of the syringe. If blood appears, follow Step 5 below.
- If no blood appears, **slowly** push the plunger in to inject your medicine.

- When the syringe is empty, take out the grey needle slowly at the same angle.
- Use your second alcohol swab to gently apply pressure where you have just injected.

5. If blood appears:

- take out the grey needle slowly at the same angle
- use your second alcohol swab to gently apply pressure where you have just pierced your skin
- empty your medicine into a sink and follow Step 6 below
- wash your hands and start again with a new vial and pre-filled syringe.

6. Disposal

- Use each needle, vial and syringe only once.
- Put the cap back on the needles so that they are safe to be thrown away.
- Ask your pharmacist how to safely dispose of used needles, vial and syringe.